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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/996,630 | 11/28/2001 | Kimberly A. Gillis | 102729-10 (AM 100491) | 3476 |

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| EXAMINER | |
|---|---|
| CHUNDURU, SURYAPRABHA | |
| **ART UNIT** | **PAPER NUMBER** |
| 1637 | |

DATE MAILED: 07/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/996,630 | GILLIS ET AL. | |
| | Examiner | Art Unit | |
| | Suryaprabha Chunduru | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *150* is/are pending in the application.

4a) Of the above claim(s) *23-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Applicants' response to the office action and amendment filed on March 10, 2004, has been entered and considered.

2. Claims 1-50 are pending. Claims 23-50 are withdrawn as being non-elected claims. Claims 1-22 are considered for examination.

### *Claim Rejections - 35 USC § 112*

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman (see In re Wands, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims".

***The nature of the invention:***

The instant claims (claim 1 and 17) are drawn to a method for assessing whether a subject is afflicted with prostrate cancer, comprising comparing (a) the level of expression of KIAA marker(s) KIAA 18 and KIAA 96 in a sample from a subject, with (b) the normal level of expression of the marker in a control sample, wherein a significant difference in the level of expression of the marker in the sample and in the normal level of expression of the marker in a control, is an indication that the subject is afflicted with prostrate cancer. The dependent claims further limitations, limiting the instant claim 1, drawn to said marker as a transcribed polynucleotide (mRNA, cDNA), said sample comprises cells from a prostate gland of a subject, level of expression said marker in a subject afflicted with prostate cancer and a control, detection of the level of expression in assessing whether a subject is afflicted with prostate cancer.

***The amount of direction or guidance presented:***

The specification discloses KIAA clones (KIAA 18 and KIAA 96) as genetic markers for this detection, diagnosis and prognosis of prostate disorders. The specification also disclose a number of other KIAA clones that encode enzymes kinases, as genetic markers for detection, diagnosis and prognosis of prostate disorders. The specification on page 10 discloses that the expression of these markers is increased (KIAA) or decreased in androgen dependent prostate cancer cells. However, the specification has not established any defined measure of statistically significant level of expression of any particular KIAA marker or a threshold level of expression beyond which a subject could be assessed as having prostate cancer. The specification fails to establish any correlation between the level of expression of KIAA markers and the prostate cancer in general because the specification discloses the expression of KIAA

markers is androgen dependent and does not provide any information regarding the expression level for other types of prostrate cancers. Further the specification provides the relative measure of the level of expression as increase or decrease relative to control samples by at least 2-, 3-,.....10-fold or more. Thus the specification fails to establish a defined level of expression threshold, which could be correlated to the development of prostate cancer in general, especially because the specification relays on the KIAA 18 and KIAA 96, of which the expression of KIAA 18 increase and the level of KIAA 96 decreases relative to control samples.

***Presence and absence of working examples***:

The specification discloses in vitro identification of a marker cDNA, by screening about 6000 full-length human genes on a chip, in response to natural androgen in LNCaP cells. The genes that showed statistically significant for treatment and interaction were considered. Further the role of KIAA (KIAA18 or KIAA 96) in solid tumors, tissue microarray analysis was performed and the gene expression using self-organizing maps were considered for classifying the expression data in response to androgen treatment. Based on the results, the specification concludes that KIAA 18 is up-regulated and KIAA 96 is down-regulated in LNCap cancer cells upon androgen treatment. The specification also discloses the differential expression of KIAA 18 and KIAA 96 in different grades of solid tumors.

The specification relays on in vitro data on the level of expression of KIAA 18 and KIAA 96. The specification does not provide any experimental data on the expression levels of KIAA 18 or KIAA 96, using samples from subjects with and without prostate cancer to assess whether a subject is afflicted with any specific prostate cancer or prostate

cancer in general. The specification has not established any statistically significant association between the level of expression of these markers in subjects with and without any specific prostate cancer.

***Level of predictability in the art***:

Predictability in the art identified a number of KIAA clones. Nagase et al. identified about 40 new KIAA genes and suggest that KIAA 0096, 0099, and 00118 were related to signal transducing genes on the basis of sequence similarities and characteristic protein motifs. Particularly, it was noted that KIAA0096 gene carries sequences with similarities to the genes in the protein kinase family (Nagase et al. DNA Res., Vol. 2, pages 37-43, 1995). An et al. disclose methods for the detection of metastatic prostate cancer by correlating the quantity of expression of a metastatic prostate cancer marker gene selected from prostate-specific transglutaminase, cytokeratin 15, or semenogelin II (US 5, 872,615). However, the art did not establish any predictable association of any of the KIAA gene markers or any other gene markers with any specific prostate cancer or the prostate cancer in general. It is apparent from the prior art that the unpredictability is high in assessing whether a subject is afflicted with any specific prostate cancer or prostate cancer in general by correlating the level of expression of any KIAA genes in general or specific KIAA 18 or KIAA 96 gene markers. In addition to the unpredictability in the art, the instant specification fails to establish any association of particular level of expression of the specific KIAA 18 or KIAA 96 in a subject with or without any specific prostrate cancer or prostate cancer in general. Given the broad scope of the instant claims, the specification does not provide any specific example that would easily predict a significant

association of the level of expression of KIAA 18 or KIAA 96 with any particular prostate cancer or prostate cancer in general.

***Qunatity of experimentation necessary***:

Given the lack of guidance in the specification and the unpredictability in the art, it would require a large amount of experimentation to practice the invention as claimed. Neither the art nor the specification provides the skilled artisan with a predictable correlation that would associate the level of these KIAA markers with any particular prostate cancer or would provide a predictable measure in assessing whether a subject is afflicted with prostate cancer. To practice the invention as claimed, the skilled artisan would have to perform a large study of patients with different types of prostate cancer and matched control subjects to determine if any general measure of the expression of these KIAA markers was associated with any specific prostate cancer or prostate cancer in general for assessing whether a subject is afflicted with prostate cancer in general based of the level of expression of these markers.

***Conclusion:***

As discussed above, the level of unpredictability is high in the art, the specification provides no guidance that would provide a predictable measure of expression of these KIAA markers in assessing whether a subject is afflicted with prostate cancer in general, one skilled in the art cannot readily anticipate the effect of change within the subject matter to which the claimed invention pertains. Thus given the broad scope of the claims in an art whose nature is identified as unpredictable, the large quantity of research is required to define these unpredictable variables. The lack of guidance in the specification,

the absence of any working examples, it would require undue experimentation for one skilled artisan to perform the method of the claimed invention as broadly written.

***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over An et al. (USPN. 5, 972,615) in view of Nagase et al. (DNA Res., Vol. 2, pages 37-43, 1995).

An et al. teach a method of 18, for detecting metastatic prostate disease state in a subject, comprising

(a) detecting in a subject sample at a first point in time the expression of KIAA marker (prostrate specific-transglutaminase) (see column 4, lines 16-25);

(c ) comparing the level of expression of step a with the level of expression in a control sample (see column 4, lines 25-35).

With regard to step (b) of the instant claim 18, An et al. also disclose that the levels of expression are measured in normal tissues or in tissue from subjects in other states (progression of disease states) of prostate disease (see column 4, lines 35-40, column 7, lines 24-34).

An et al. also teach that the sample comprises cells obtained from a subject (see column 4, lines 16-19); cells collected from prostate tissue (see column 4, lines 16-19); and cells collected from blood (see column 27, lines 1-8).

However, An et al. did not specifically teach expression of KIAA 18 or KIAA 96.

Nagase et al. teach a method of screening about 40 KIAA markers which includes KIAA 096), wherein Nagase et al. teach that KIAA096 gene carries sequences with similarities to the genes in protein kinase family and is related to signal transducing genes (see page 40, column 1, lines 9-16).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to modify a method for detecting the expression of KIAA markers as taught by An et al. with the teachings of KIAA 96 as taught by Nagase et al. to achieve expected advantage of developing an improved method fro monitoring the progression of prostate cancer in a subject disease because Nagase et al. taught the role of KIAA 96 in signal transduction and similarities with protein kinase gene family (see page 40, column 1, lines 9-16). Thus an ordinary practitioner would have motivated to combine the method of detecting and monitoring the progression of prostate cancer in a subject as taught by An et al. with the addition of the step of specific

KIAA markers involved in signal transduction pathway as taught by Nagase et al. which would result in developing an improved and sensitive method which would provide a better prognosis of prostate cancer.

***Response to arguments***

5. Applicants' response to the office action is fully considered and found persuasive in part.

6. The following is the rejection made in the previous office action under 35 USC 112, second paragraph:

Claims 1-22 are rejected over the abbreviated term "KIAA". The abbreviation has not been explained in the specification or in the claims. In absence of the fully explained abbreviation of the term "KIAA", it is not clear what is meant or encompassed by "KIAA markers" of the instant invention. The meets and bounds of the claims are vague and indefinite.

***Response to arguments***:

With reference to the above rejection applicants' arguments and amendment are fully considered and found not persuasive. Applicants amended the claims as KIAA 18 and KIAA 96 and direct examiner's attention to a particular page of the instant specification. As noted in MPEP 2145, "Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims". In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993), the instant claims do not recite

what KIAA 18 or KIAA 96 is meant and specification is not being read into the claims. Thus the rejection is maintained herein.

7. With reference to the rejection made in the previous office action under 35 USC 102(b), applicants' arguments and amendment are fully considered and the rejection is withdrawn in view of the amendment.

8. With reference to the rejection made in the previous office action under 35 USC 103(a), applicants' arguments and amendment are fully considered and the rejection is in view of the arguments and new grounds of rejections.

***Conclusion***

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and - for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Suryaprabha Chunduru
July 1, 2004

JEFFREY FREDMAN
PRIMARY EXAMINER
7/2/04